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Muscarinic M1 receptor modulation of cognition using a translational approach : relevance for dementia and schizophrenia

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SUMMARY

One of the main research themes in psychology and neuroscience is cognitive dysfunction, which usually occurs as an epiphenomenon of brain diseases and/or neuropsychiatric disorders. Unfortunately, patient heterogeneity makes it difficult to correlate cognitive deficits with specific neurobiological findings. Therefore, a lot of effort is dedicated to mimicking cognitive impairments with pharmacological tools that temporarily impact neurotransmission in healthy animals and young volunteers (Gilles & Luthringer, 2007).

The non-selective cholinergic (i.e., muscarinic) antagonist scopolamine has been employed extensively as a standard/reference drug to induce age- and dementia-related impairments in cognitive function. The guiding principle for its use has been the cholinergic hypothesis of geriatric memory dysfunction, which assumes that the age-related decline in cognitive functions is predominantly related to a decrease in the integrity of cholinergic neurotransmission (Bartus et al., 1982). However, an exclusive role for acetylcholine in geriatric memory dysfunction can be viewed as too restrictive, as cholinergic impairments have also been noted in schizophrenia (Sarter et al., 2012). Thus, the question arises whether aberrant cholinergic signaling might be a common neuropathological pathway underlying aging, dementia and schizophrenia, and whether administration of cholinergic (i.e., muscarinic) antagonists might hence serve as a model for cognitive impairments associated with these disorders.

Chapter 2 has provided an overview of the effects of scopolamine on animal behavior. It appears that behavioral paradigms which assess stimulus discrimination and/or (sustained) attention processes are relatively more sensitive to impairments induced by the muscarinic antagonist scopolamine compared to tasks which measure learning/memory functions (i.e., effects at relatively lower doses). These findings have spurred a lot of debate on the specific role of acetylcholine in cognition – i.e. on learning/memory vs. attention (Hasselmo, 1999; 2006; Hasselmo et al., 2002; Hasselmo & McGaughy, 2004; Sarter et al., 2003; 2005; 2009). It is concluded that effects on learning and memory performance which are observed after higher doses of scopolamine are mediated by 1) primary effects on attention and sensory/stimulus discrimination, 2) non-specific effects on behavior (locomotor activity, anxiety), and 3) peripheral side-effects (pupil dilation, salivation). Finally, the validity of scopolamine as a pharmacological model for cognitive impairment is questionable, as its non-selectivity with regards to muscarinic receptors complicates interpretation of behavioral findings. On the basis of the distribution of the muscarinic M_1 receptor in the brain and body (Caulfield, 1993), muscarinic M_1 antagonists are put forward as a more selective and effective way of inducing cholinergic deficits.

The study in **Chapter 3** investigated in rats whether the muscarinic M_1 receptor antagonist biperiden would induce more selective effects on a battery of operant tasks: i.e., fixed ratio and progressive ratio schedules of reinforcement, an attention paradigm and delayed non-matching to position task. Scopolamine was found to disrupt performance in all behavioral paradigms. Biperiden induced relatively more selective deficits; it had no effect on food motivation or attention, and effects on psychomotor performance and working memory were dissociable based on dose conditions (i.e., 10 mg/kg and 3 mg/kg, respectively). It was concluded that muscarinic M_1 antagonists such as biperiden should be considered as a pharmacological model for cholinergic mnemonic deficits in animals, due to their selectivity with regards to mnemonic effects.

The goal of the study in **Chapter 4** was to assess the selectivity of the muscarinic M_1 antagonist biperiden with regards to verbal memory, psychomotor performance and self-reports of side-effects in young, healthy human volunteers. After biperiden, participants recalled on average about 4 words less on the immediate and delayed recall of the verbal learning task. Word recognition scores in the verbal recognition task were reduced by 8% after biperiden. Biperiden did not influence reaction times in a verbal recognition task or a choice reaction time task, which is indicative of a lack of psychomotor effects. There was also no effect of biperiden on accuracy in the choice reaction time task, nor did participants report experiencing any side-effects. It was concluded that biperiden is capable of impairing verbal memory rather selectively, i.e., without inducing clear peripheral side-effects which could adversely affect performance.

The study in **Chapter 5** investigated the effects of the muscarinic M_1 antagonist biperiden on a within-subject learned irrelevance (LIrr) paradigm and event-related potentials (ERPs) in humans. LIrr refers to a reduction in associative learning after pre-exposure of the conditioned (CS) and unconditioned stimulus (US) in a non-contingent fashion (Baker, 1976; Mackintosh, 1973). This paradigm might serve as a translational model for (pre)attentive information processing deficits in schizophrenia controls (Gal et al., 2005; Orosz et al., 2011; Young et al., 2005). Given the involvement of the cholinergic system in the pathophysiology of schizophrenia (Sarter et al., 2012), it was hypothesized that biperiden would disrupt LIrr performance. Unexpectedly, biperiden had no effect on the behavioral LIrr measures, although prolonged reaction times were evident. The N1 amplitude of the pre-exposed (PE) predictor letters was increased after biperiden, suggesting an effect of this drug on early perceptual processing. In conclusion, the within-subject paradigm used in the current study in combination with ERPs can reveal brain mechanisms involved in LIrr. M_1 antagonism does not appear to be involved in LIrr deficits as reported in schizophrenia.

The study described in **Chapter 6** assessed the effects of the non-selective muscarinic antagonist scopolamine, the muscarinic M_1 antagonist biperiden, the cholinesterase inhibitor donepezil and their combination on auditory evoked potentials (AEPs) and sensory gating in rats. As perturbations in auditory filtering appear to be a candidate trait marker of schizophrenia (Cadenhead et al., 2000; Olincy et al., 2010; Simons et al., 2011), there has been considerable interest in the development of translational rat models to elucidate the underlying neural and neurochemical mechanisms involved. Scopolamine and biperiden both disrupted sensory gating by increasing N1 amplitude for the S2 click. Scopolamine also affected the latencies of the P1, N1 and P2 peaks. Donepezil was able to fully reverse the effects of biperiden on N1 sensory gating, but had residual effects when combined with scopolamine (i.e., enhancement of sensory gating). Donepezil by itself improved sensory gating by increasing N1 amplitude of S1, and reducing N1 amplitude of the S2 click. In conclusion, due to its relatively more selective effects, biperiden is to be preferred over scopolamine as a means for pharmacologically inducing impairments in auditory processing in healthy rats.

The goal of the study in **Chapter 7** was to investigate the effects of the muscarinic M_1 antagonist biperiden and the cholinesterase inhibitor rivastigmine on AEPs, sensory gating and mismatch negativity (MMN) in young, healthy volunteers. Suppression of redundant auditory information and facilitation of deviant, novel or salient sounds can be assessed with paired-click and oddball tasks, respectively (Boutros et al., 2004; Garrido et al., 2009; Näätänen et al., 2004; Pekkonen et al., 2005). Electrophysiological correlates of perturbed

auditory processing found in these paradigms are likely to be a trait marker for schizophrenia (Cadenhead et al., 2000; Olincy et al., 2010; Price et al., 2006; Simons et al., 2011). Biperiden increased P50 amplitude and prolonged N100 and P200 latency in the paired-click task.[7] Rivastigmine was able to reverse the effects of biperiden on N100 and P200 latency. Biperiden increased P50 latency in the novelty oddball task, which was reversed by concurrent administration of rivastigmine. Rivastigmine shortened N100 latency and enhanced P3a amplitude in the novelty oddball paradigm, both of which were reversed by biperiden. It was concluded that the muscarinic M_1 receptor appears to be involved in pre-attentive processing of auditory information.

Taken together, effects of biperiden on behavior in rats and humans can be characterized as follows: 1) primary effects on learning/memory– which are likely mediated by blockade of postsynaptic muscarinic M_1 receptors in the hippocampus (**Chapters 2, 3 and 4**) and 2) non-specific central effects on psychomotor slowing – which are likely mediated via muscarinic M_1-dopamine interactions in striatum (see **Chapters 2-5** and De Klippel et al., 1993; Gerber et al., 2001; Thomsen et al., 2010). Peripheral side-effects are limited compared to scopolamine – i.e., at low doses there are minor to no effects on salivation or sedation (**Chapters 2-5 and 7**).

With respect to ERPs, biperiden generally induces increments in the amplitudes of early perceptual components (i.e., N1 in rats, and P50 and N100 in humans, see **Chapters 6 and 7**). Thus, effects of biperiden on behavior appear to be focused on mnemonic functions, whereas those on ERPs seem to be more related to attentional processes. This discrepancy is possibly due to primary effects of biperiden on memory, and secondary on attention. It appears that muscarinic M_1 modulation of cognition is complex and dependent on brain region.

We have also found some different findings between species with respect to our EEG studies – i.e., disruption of hippocampal sensory gating in rats vs. a lack of effect of biperiden on human sensory gating. We presume that differences in methodology, especially with respect to the sensitivity of the EEG equipment to pick up on hippocampal activity, underlie the discrepancies between species. Furthermore, some progress has been made with respect to determining the pharmacodynamic and pharmacokinetic properties of scopolamine and biperiden in humans vs. rats. However, a direct comparison of plasma and brain concentrations at various doses of scopolamine and biperiden and in several species is currently lacking, which is pertinent in order to be able to compare effective dose ranges used in translational research.

In contrast to our findings in **Chapters 6 and 7**, most studies investigating sensory gating in schizophrenia have reported impaired P50 suppression due to a reduction of the initial P50 response to S1 (Jin & Potkin, 1996). However, in aging and age-related disorders such as mild cognitive impairment and Alzheimer's disease, an increase in amplitudes of early AEP components (Golob et al., 2001a; 2001b; Irimajiri et al., 2005) and reduced sensory gating due to an increase in P50 amplitude of the S2 click has also been reported (Cancelli et al., 2006; Jessen et al., 2001; Thomas et al., 2010). Therefore, changes in auditory processing and sensory gating induced by muscarinic drugs may serve as a translational model for aging rather than schizophrenia.

[7] The effect on P200 latency in the paired-click task in **Chapter 7** was interpreted as reflective of a downstream effect on the N100 (cf. Simons et al., 2011).

Future research should replicate/confirm the selective effects of biperiden compared to scopolamine, especially with respect to findings of mnemonic but not attentional deficits after biperiden. Moreover, it is pertinent that biperiden is tested in memory paradigms along with recording of EEG, to assess whether it would influence mnemonic ERP components such as the P300 (particularly the P3b: Polich & Criado, 2006). In this respect, the development of ligands which are more selective for a particular muscarinic receptor subtype would be an important step in determining muscarinic receptor modulation of cognition. However, this has been challenging due to the highly conserved orthosteric acetylcholine binding site of muscarinic receptors (Bolden et al., 1992; Heinrich et al., 2009). Nevertheless, selective muscarinic M_1-M_5 antagonists need to be perceived as additional pharmacological tools besides the golden standard scopolamine to elucidate muscarinic receptor modulation of cognition and behavior.

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